A Versatile New Synthesis of Quinolines and Related Fused Pyridines. Part 7.[1] The Conversion of Acetamidothiophens into Thienopyridines

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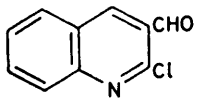
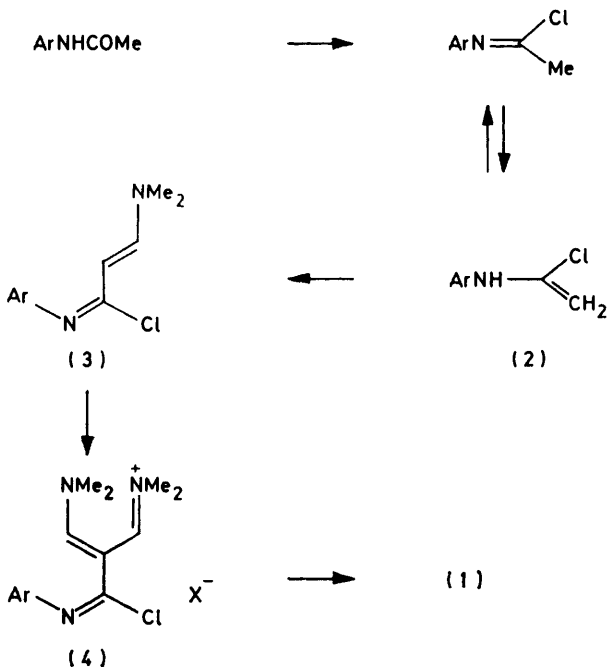
5-Substituted-2-acetamidothiophens are converted into 2-acetamidothiophen-3-carbaldehydes in good yield with equimolar amounts of dimethylformamide and phosphoryl chloride in hot dichloroethane. However, under similar conditions but with three mol of phosphoryl chloride, 6-chlorothieno[2,3-*b*]pyridines are obtained. Use of phosphoryl chloride as solvent (7 mol) with three mol of dimethylformamide gives good yields of 6-chlorothieno-[2,3-*b*]pyridine-5-carbaldehydes. Similarly, thieno[3,2-*b*]- and thieno[3,4-*b*]-pyridines are obtained from 3-acetamidothiophen and 2,5-dimethyl-3-acetamidothiophen respectively. The mechanisms of these reactions are explored and compared with those involved in the formation of related quinolines from acetanilides and shown to involve initial ring formylation. The analogous formation of 2-chloroquinolines is shown to have limited potential.

In an earlier paper [2] we demonstrated that 2-chloroquinoline-3-carbaldehydes (1) could be readily made by treatment of acetanilides with dimethylformamide



(1)

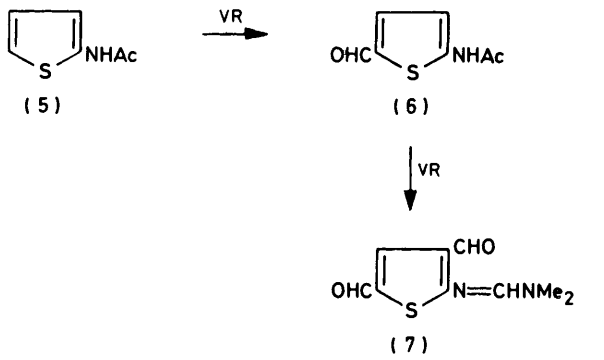
(DMF) and phosphoryl chloride (Vilsmeier's reagent, VR). The reaction involved the successive conversions outlined in Scheme 1, the crucial stages being the formylation of the enamines (2) and (3) We [3a] and others [3b]



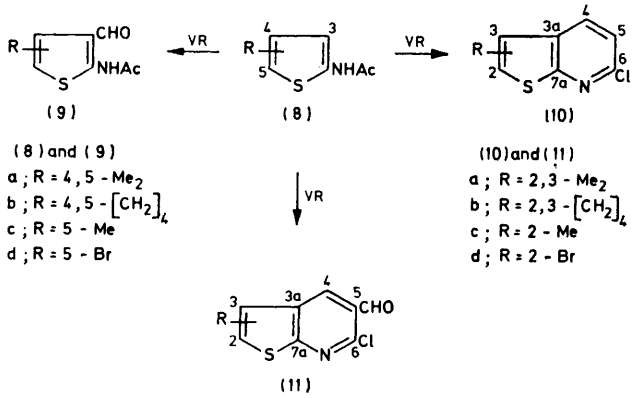
Scheme 1

have already shown that a similar formylation of 2-acetamidothiophen (5) results in ring formylation to give the 5-carbaldehyde (6) under mild conditions and the 3,5-dicarbaldehyde (7) under more vigorous conditions, there being no evidence of thienopyridine formation. We herein describe our endeavours to synthesise thienopyridines by Vilsmeier formylation of acetamidothiophens.

Shvedov and his co-workers [4] have shown that several 5-substituted-2-acetamidothiophens (8) are converted



into the corresponding 3-carbaldehydes (9) with VR in fair yield. However, we found that careful chromatography of a typical product [from (8a)] showed the presence of the chlorothienopyridine (10a) (32%) and the corresponding aldehyde (11a) (2%) in addition to the expected product (9a) (48%). We therefore developed conditions that would allow each product to be formed optimally.



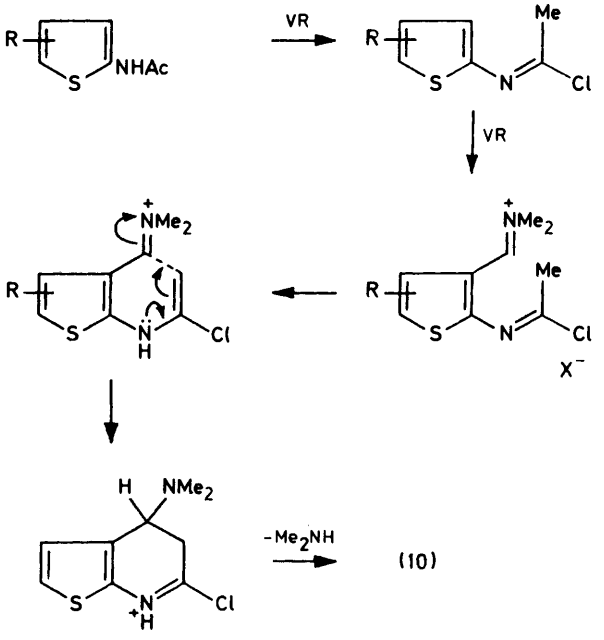
Scheme 2

Formation of 2-Chlorothienopyridines (10) *and of Acetamidothiophencarbaldehydes* (9).—The readily available acetamidothiophen (8b)[5] was subjected to formylation under a variety of conditions, in which the ratio of DMF : $POCl_3$, and the reflux time for the reaction was varied (Table 1). In no case was any chloropyridine-carbaldehyde (11) produced under these conditions while optimum chloropyridine (10) formation (80%) was derived from prolonged heating with an excess of phosphoryl chloride (*i.e.* at least 3 mol per mol of substrate and DMF). Brief reaction with an equimolar ratio of reactants gave optimum yields of the acetamidocarbaldehyde (9). Thus, unlike the acetanilides, initial ring formylation rather than side-chain formylation leads to the pyridine ring as outlined in Scheme 3. We and others have already demonstrated that the formation of imidoyl chloride occurs rapidly even in the cold and that the subsequent acid-catalysed tautomerism is involved in this type of reaction.[6]

TABLE 1

Products from the formylation of 2-acetamido-4,5,6,7-tetrahydro-1-benzothiophen (8b) with VR in 1,2-dichloroethane

Reaction conditions			Products (%)	
DMF (mol equiv.)	$POCl_3$ (mol equiv.)	Reflux time (min)	Aldehyde (9b)	Chloropyridine (10b)
1	1	15	76	12
1	1	60	68	19
1	2	15	65	24
1	2	60	16	58
1	3	60	8	80
1	4	60	8	78



SCHEME 3

A variety of acetamidothiophens were subjected to these optimum conditions, the reaction being followed by t.l.c. on alumina plates. The less reactive substrates were best converted into products in the higher-boiling 1,1,2,2-tetrachloroethane and the results are collected in Table 2.

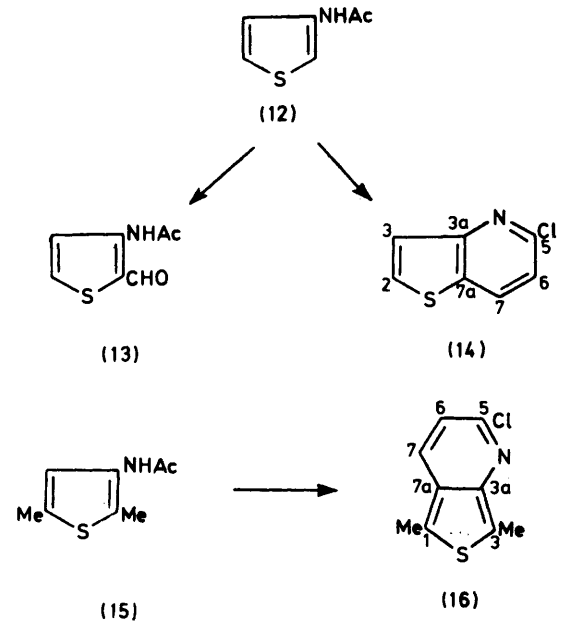
TABLE 2

Products from the action of VR on various acetamidothiophens

Substrate	Reaction conditions: DMF (mol equiv.)	$POCl_3$ (mol equiv.)	Solvent *	t/h	Product [%]
(8c)	1	1	A	0.5	(9c) [62]
(8c)	1	3	A	6	(10c) [79]
(8d)	1	3	B	12	(10d) [66]
(8a)	1	1	A	0.33	(9a) [72]
(8a)	1	3	A	5	(10a) [72]
(8b)	1	1	A	0.25	(9b) [79]
(8b)	1	3	A	4	(10b) [79]
(12)	1	1	A	0.25	(13) [88]
(12)	1	3	A	4	(14) [70]
(15)	1	3	A	6	(16) [52]

* A = 1,2-Dichloroethane; B = 1,1,2,2-tetrachloroethane.

The efficient conversion of acetamidothiophens specifically into the corresponding aldehydes (of great value for further derivatisation or ring-closure [4]) or into chlorothienopyridines is underlined. As well as the synthesis of thieno[2,3-*b*]pyridines (10), the formation of the [3,2-*b*]- and [3,4-*b*]-analogues (14) and (16), respectively, is particularly noteworthy. Indeed these methods constitute the easiest general source of simple thienopyridines yet available. The rare quinonoidal thienopyridine (16) proved to be unstable, as noted by other workers for this system.[7]



Formation of Chlorothienopyridinecarbaldehydes (11).—In the benzene series, we found that use of phosphoryl chloride as reaction solvent allowed conversion of acetanilides into 2-chloroquinoline-3-carbaldehydes in

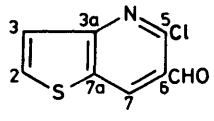
high yield by the action of VR.[2] Similar results were observed in the thiophen series although we interpret the reaction pathway differently (Table 3).

TABLE 3

Formation of thienopyridine aldehydes (11), (17), and (18) from the action of DMF (3 mol equiv.) and $POCl_3$ (7 mol equiv.) on acetamidothiophens (8), (12), and (15)

Substrate	Reflux time/h	Product [%]
(8c)	3	(11c) [62]
(8d)	4	(11d) [66]
(8a)	2	(11a) [73]
(8b)	2	(11b) [88]
(12)	1.5	(17) [72]
(15)	1.5	(18) [39]

Again the isomeric series (17) and (18) were available as the [2,3-*b*]-fused thienopyridinecarbaldehydes. We interpret these reactions as outlined in Scheme 4, involving first ring formylation followed by side-chain



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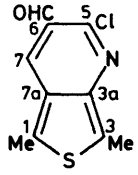
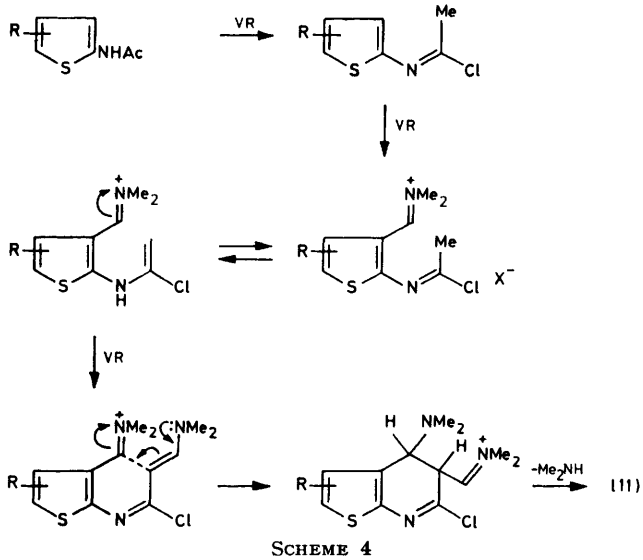


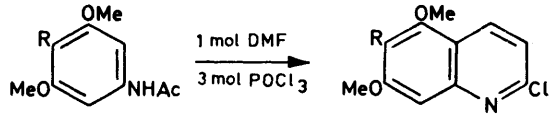
(18)

formylation prior to ring-closure. A blank experiment showed that the chlorothienoquinolines (10) were not formylated to give the corresponding aldehydes (11), but remained unchanged under the reaction conditions.



SCHEME 4

The principal difference in mechanism between the acetanilides and the acetamidothiophens is in the site of initial formylation. In order to synthesise 2-chloroquinolines, we argued that given sufficient activation an acetanilide should undergo ring rather than side-chain formylation. However, despite initial claims of success in our preliminary publication [1] later work has shown that this is by no means easily achieved. Indeed, only 3,5-dimethoxyacetanilide (19a) and to a lesser extent

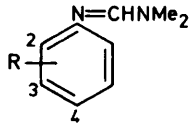


(19) (20)

R = H, 55%
R = OMe, 10%

a, R = H; b, R = OMe

3,4,5-trimethoxyacetanilide (19b) showed any tendency to cyclise to a chloroquinoline (20). 3-Methoxy- and 3-methyl-acetanilide as well as acetanilide itself, did not give chloroquinolines, but only the corresponding formamidines (21) which we have already noted to be a



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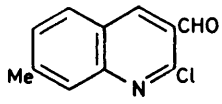

(22)

sign of insufficient reactivity for quinoline formation.[2] In the absence of a co-solvent such as di- or tetrachloroethane, when only one mol of DMF is utilised per mol of the acetanilide, a low yield of the 2-chloroquinoline-3-carbaldehyde [*e.g.* (22)] is obtained, showing that only side-chain formylation [the second formylation step being faster than the first (see ref. 2)] is occurring.

EXPERIMENTAL

The general conditions are as outlined in Part 5.[2]

Synthesis of Acetamidothiophens (8), (12), *and* (15).—2- and 3-Acetamidothiophen, 2-acetamido-5-methyl-, 2-acetamido-5-bromo-, and 2,5-dimethyl-3-acetamido-thiophen were all made by the Beckmann reaction on the corresponding acetoxime as described elsewhere.[3a] 4,5-Dimethyl- and 4,5-tetramethylene-2-acetamidothiophen were made by Shvedov's method.[5]

Synthesis of Acetamidothiophencarbaldehydes (9) *and* (13) *and Chlorothienopyridines* (10), (14), *and* (16).—*General method.* Dimethylformamide (2.74 g, 0.0375 mol) was cooled to 0 °C in a flask equipped with a drying tube and phosphoryl chloride (5.76 g, 3.5 ml, 0.375 mol, or otherwise as in Tables 1 and 2) was added dropwise with stirring. To this solution was added redistilled 1,2-dichloroethane or 1,1,2,2-tetrachloroethane (25 ml) followed by a solution of the acetamidothiophen (0.0375 mol) in the same chloroethane solvent (75 ml). The mixture was stirred at room temperature for 15 min and then refluxed for an appropriate time (see Tables 1 and 2). The cooled solution was poured onto ice (*ca.* 300 g) with stirring and sodium acetate (8.2 g, 0.1 mol) added, and the mixture was boiled for 20 min, cooled, and separated. The aqueous phase was extracted with dichloromethane and the combined organic

TABLE 4

Properties of the products (9)—(11), (13), (14), and (16)—(18)

Compound	Recryst. solvent †	M.p./°C	Lit. m.p./°C	Ref.	Found C	Found H	Found N	Formula	Required C	Required H	Required N	$\nu_{max.}$ NH	$\nu_{max.}$ CHO	$\nu_{max.}$ COMe
(9a)	A	136	134—135	4								3 250	1 680	1 645
(9b)	B	124 (decomp.)	123—124	4								3 250	1 680	1 640
(9c)	B	85—86										3 260	1 710	1 660
(10a)	C	90.5—91			54.7	4.2	7.0	C_9H_8ClNS	54.7	4.7	7.1			
(10b)	C	64—65			58.7	4.6	6.25	$C_{11}H_{10}ClNS$	59.05	4.5	6.3			
(10c)	C	65			52.5	3.3	7.4	C_8H_6ClNS	52.3	3.3	7.6			
(10d)	A	115—116			38.85	1.2	5.6	$C_7H_3BrClNS$	33.8	1.2	5.6			
(11a)	B	157			53.4	3.5	6.4	$C_{10}H_8ClNOS$	53.2	3.6	6.2		1 690	
(11b)	B	145			57.2	4.1	5.7	$C_{13}H_{10}ClNOS$	57.25	4.0	5.6		1 690	
(11c)	B	127			51.2	2.8	6.5	C_9H_6ClNOS	51.1	28.5	6.6		1 690	
(11d)	B	170			34.7	1.2	5.25	$C_8H_3BrClNOS$	34.75	1.1	5.1		1 680	
(13)	B	72 (decomp.)	72	*a*								3 250	1 680	1 640
(14)	D	63—64	64	*b*										
(16) *	C	158												
(17)	B	122	122	*b*									1 680	
(18)	B	146			53.2	3.5	6.2	$C_{10}H_8ClNOS$	53.2	3.6	6.2		1 680	

* This product rapidly deteriorated and was not analysed. † A = Ethanol; B = ethyl acetate; C = aqueous ethanol; D = sublimation.

[a] G. Ah-Kow, C. Paulmier, and P. Pastour, *Bull. Soc. Chim. Fr.*, 1976, 151. [b] C. Paulmier and F. Outurquin, *J. Chem. Res.* (*S*), 1977, 318; (*M*), 1977, 3660.

TABLE 5

N.m.r. spectral characteristics of the products (9)—(11), (13), (14), and (16)—(18)

Compd.	^{1}H Chemical shifts (δ) 2-H	3-H	4-H	5-H	6-H	7-H	Others	*J*/Hz	^{13}C Chemical shifts (δ) C-2	C-3	C-4	C-5	C-6	C-7	Others
(9a)							2.13(s), 2.17(s, 2Me), 11.60(b, NH), 9.77(s, CHO)		148.6	120.5	123.7	128.0			183.6(CHO), 167.7(CO), 23.4(CO*Me*), 11.8(5-Me), 11.0(4-Me)
(9b)							1.81(m), 2.78(m, $[CH_2]_4$), 2.27(s, Me), 9.80(s, CHO)		149.3	119.5	127.0	130.2			185.9(CHO), 167.8(CO), 23.2(CO*Me*), 22.2, 23.05, 23.5, 23.9
(9c)			6.73(s)				2.27(s, Me), 2.35 (COMe), 9.70(s, CHO), 11.80br (NH)		148.1	121.8	121.8	130.2			186.4(CHO), 167.7(CO), 23.1(CO*Me*), 14.4(Me)
(10a)			7.49(d)	6.98(d)			2.05(s), 2.29(s, 2Me)	$J_{4,5}$ 8	133.0	119.3	130.2	124.6	146.3		159.3(C-7a), 134.7(C-3a), 13.7(2-Me), 10.8(3-Me)
(10b)			7.47(d)	7.03(d)			1.83, 2.50, 2.70 ($[CH_2]_4$),	$J_{4,5}$ 8	131.5	126.8	129.2	119.1	146.0		159.8(C-7a), 137.7(C-3a), 21.9, 23.0, 25.4, 25.4
(10c)	6.76		7.73(d)	7.13(d)			2.53(s, Me)	$J_{4,5}$ 8	132.6	118.7	131.8	119.8	146.3		160.6(C-7a), 141.9(C-3a), 16.4(Me)
(10d)	7.27(s)		7.88(d)	7.28(d)				$J_{4,5}$ 8	114.3	118.2	129.3	121.1	145.2		158.6(C-7a), 129.3(C-3a)
(11a)			8.17(s)				10.58(s, CHO), 2.35(s), 2.55(s, 2Me)		133.9	124.6	129.5	125.8	148.6		164.0(C-7a), 136.9(C-3a), 189.6(CHO), 16.1, 11.1(Me)

TABLE 5 (*continued*)

Compd.	^{1}H Chemical shifts (δ) 2-H	3-H	4-H	5-H	6-H	7-H	Others	*J*/Hz	^{13}C Chemical shifts (δ) C-2	C-3	C-4	C-5	C-6	C-7	Others
(11b)			8.17(s)				10.58(s, CHO), 1.95 2.78 ([CH$_2$]$_4$)		132.6	124.4	128.7	128.1	148.1		164.5(C-7a), 140.1(C-3a), 189.2(CHO), 25.6, 23.1, 23.1, 21.8 (4 × CH$_2$)
(11c)		6.62(s)	8.40(s)				10.80(s, CHO), 2.40(s) (2Me)		132.9	119.1	130.7	124.7	147.8		164.8(C-7a), 143.8(C-3a), 188.8(CHO), 16.5(Me)
(11d)		7.36(s)	8.41(s)				10.43 (CHO)		132.8	117.1	127.6	125.7	147.7		164.0(C-7a), 144.8(C-3a), 188.9(CHO)
(13)			8.25(d)	7.76(d)			2.25(s, Me), 9.80(s, CHO), 11.72br (NH)	$J_{4,5}$ 5							
(14)	7.70(d)	7.40(d)			7.17(d)	7.99(d)		$J_{2,3}$ 5 $J_{6,7}$ 5 $J_{2,7}$ 0.7 $J_{3,6}$ 0.4	124.3	118.1		139.8	123.1	131.7	130.6(C-7a), 154.5(C-3a)
(16)					7.12(d)	7.86(d)	2.86(s, 2Me)	$J_{6,7}$ 8		132.7		135.3	123.2	129.4	132.4(C-1), 130.5(C-7a), 148.3(C-3a), 12.46, 10.48 (2 × Me)
(17)	8.10(d)	7.49(dd)				8.77(d)	10.58(s, CHO)	$J_{2,3}$ 6 $J_{3,7}$ 1	134.1	123.6		149.3	123.3	132.1	189.0(CHO), 140.4(C-7a), 157.8(C-3a)
(18)						8.30(s)	10.37(s, CHO), 2.70(s, 2Me)			135.8		146.8	122.5	126.0	188.9(CHO), 140.3(C-7a), 144.0(C-3a), 135.6(C-1)

phases were washed with saturated aqueous sodium hydrogen carbonate. After drying ($MgSO_4$) the solution was evaporated and chromatographed on alumina. Elution with light petroleum gave the chlorothienopyridine while a mixture of light petroleum and chloroform (4 : 1 v/v) gave the acetamidothiophencarbaldehyde (see Tables 1 and 2). The properties of the products are recorded in Tables 4 and 5.

Synthesis of Chlorothienopyridinecarbaldehydes (11), (17), *and* (18).—To the Vilsmeier complex prepared from dimethylformamide (5.5 g, 0.075 mol) and phosphoryl chloride (26.9 g, 16.0 ml, 0.175 mol) was added the acetamidothiophen (0.025 mol) and the mixture was stirred at room temperature for 15 min. The mixture was heated under reflux for an appropriate time (Table 3), cooled, and poured onto ice (*ca.* 200 g) with vigorous stirring. The solution was neutralised with aqueous sodium hydroxide (40%) with ice cooling and the precipitate was filtered off, washed with water, and dried by suction. Recrystallisation from ethyl acetate gave the products recorded in Tables 3, 4, and 5.

Synthesis of Chloroquinolines (20).—To the Vilsmeier complex prepared from dimethylformamide (1.46 g, 1.55 ml, 0.02 mol) and phosphoryl chloride (9.21 g, 5.5 ml, 0.06 mol) in 1,2-dichloroethane (150 ml) at 0 °C was added 3,5-dimethoxyacetanilide (3.70 g, 0.02 mol) with stirring. The solution was heated under reflux for 4.5 h, cooled, and poured onto ice–water (*ca.* 300 ml), made alkaline (pH 9) with aqueous sodium hydroxide (40%), and stirred for 0.5 h. The aqueous phase was extracted with dichloromethane (50 ml) and the combined organic phase was dried ($MgSO_4$) and evaporated to give a red solid. Chromatography on alumina with toluene as eluant gave *2-chloro-5,7-dimethoxyquinoline* (20a) (2.45 g, 55%) as white needles, m.p. 134—135 °C (from ethanol) (Found: C, 59.1; H, 4.5; N, 6.1. $C_{11}H_{10}ClNO_2$ requires C, 59.1; H, 4.5; N, 6.3%), $\nu_{max.}$ (Nujol) 1 630, 1 590, 1 240, 1 205, 1 170, 1 130, 820, and 805 cm^{-1}, δ ($CDCl_3$) 8.27 (d, H-4), 7.14 (d, H-3), 6.89 (d, H-8), 6.45 (d, H-6), 3.90 (s, MeO), and 3.88 (s, MeO) ($J_{3,4}$ 9, $J_{6,8}$ 3 Hz).

Similarly from 3,4,5-trimethoxyacetanilide (2.25 g, 0.01 mol) was obtained *2-chloro-5,6,7-trimethoxyquinoline* (0.25 g, 10%) by elution with light petroleum. The product was recrystallised from ethanol as white needles, m.p. 97.5—98.5 °C (Found: C, 57.0; H, 4.7; N, 5.6. $C_{12}H_{12}ClNO_3$ requires C, 56.8; H, 4.8; N, 5.5%), $\nu_{max.}$ (Nujol) 1 620, 1 580, 1 400, 1 120, and 805 cm^{-1}, δ ($CDCl_3$) 8.30 (d, H-4), 7.24 (d, H-3), 7.19 (s, H-8), 4.08 (s, MeO), 4.00 (s, MeO), and 3.98 (s, MeO) ($J_{3,4}$ 9 Hz).

Similar treatment of 3-methylacetanilide and 3-methoxyacetanilide gave after the above work-up (*a*) *NN*-dimethyl-*N'*-(3-methylphenyl)formamidine (21; R = 3-Me) (29%) as a pale yellow oil, b.p. 124—126 °C at 0.05 mmHg (Kugelrohr), (lit.[8] 78—79 °C at 0.05 mmHg), $\nu_{max.}$ 2 910, 1 630 (C=N), 1 590, 1 570, 1 090, 770, and 690 cm^{-1} (*meta*-subst.), δ ($CDCl_3$) 7.46 (s, CH=N), 7.25—7.0 (m, 1 × ArH), 6.9—6.65 (m, 3 × ArH), 2.92 (s, Me_2N), and 2.28 (s, Me); and (*b*) *N'*-(3-methoxyphenyl)-*NN*-dimethylformamidine (21; R = 3-MeO), (51%) as a pale yellow oil, b.p. 150 °C at 0.2 mmHg (Kugelrohr) (lit.[9] 164 °C at 12 mmHg, $\nu_{max.}$ 1 930, 1 640

(C=N), 1 590, 770, and 700 cm^{-1} (*meta*-subst.), δ ($CDCl_3$) 7.48 (s, CH=N), 7.20—7.00 (m, H-5), 6.65—6.45 (m, 3 × ArH), 2.90 (s, Me_2N), and 3.71 (s, MeO).

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